Quantifying common adverse effects of a drug used for any indication from RCTs: the example of amoxicillin

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Quantifying common adverse effects of a drug used *for any indication* from RCTs: the example of amoxicillin

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why we did the review

- antibiotic resistance crisis
- primary care focus
- need to reduce antibiotics for common ARIs

  apart from resistance, antibiotic…

  - …minimal benefit
  - …have common harms

    -- but poorly quantified

  amoxicillin +/- clavulinate

antibiotic resistance

- tonnage antibiotics ➔ ¾ in primary care

- opportunity for *shared decision making*
- need common harms data

how AEs are usually measured

- secondary outcomes of RCTs

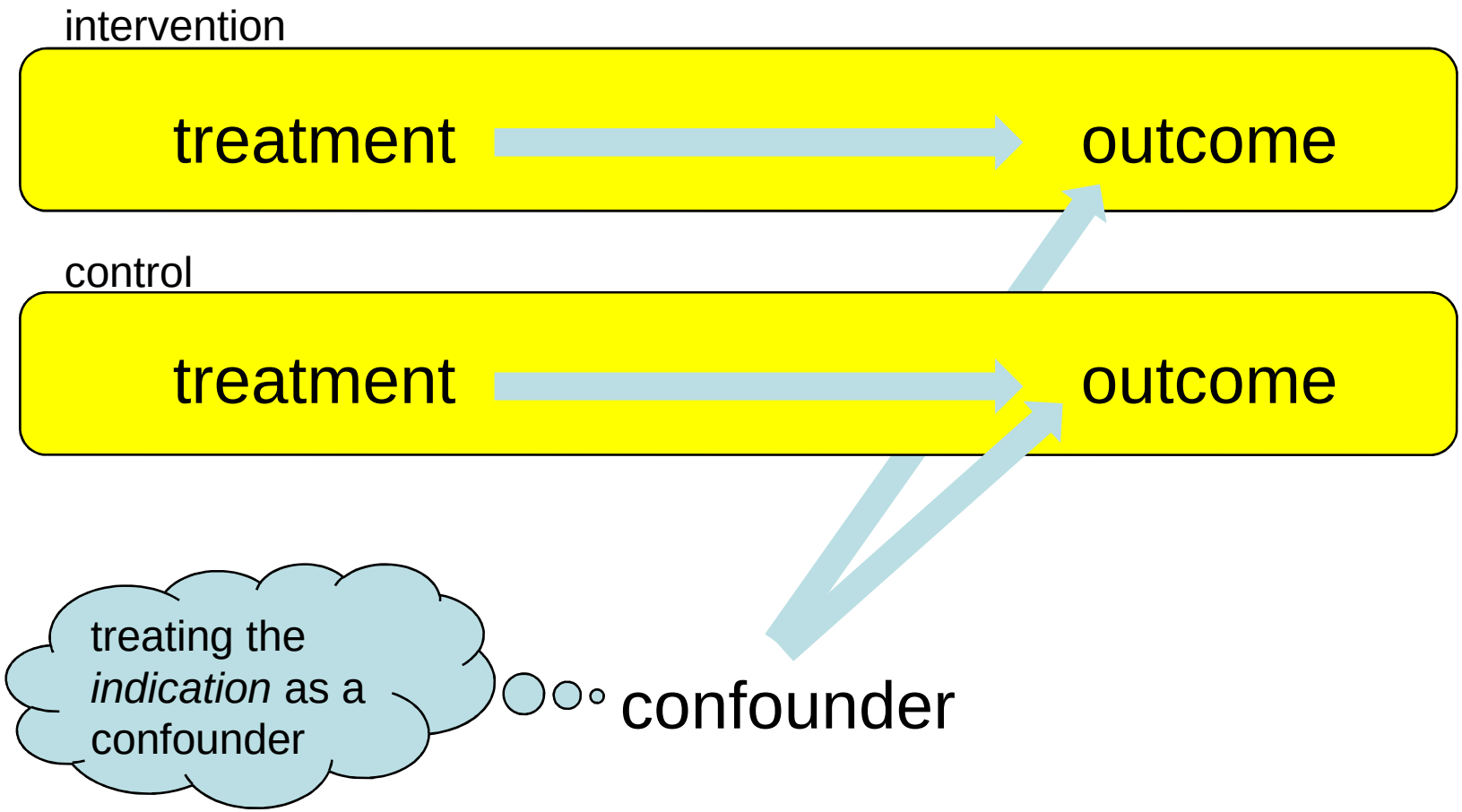
BUT rarer events, so underpowered

- observational studies
  - post-marketing surveillance
  - national AEs voluntary reporting
  - other observational studies

BUT confounders…

dealing with confounding

randomisation



what we did

PICO

P – *any* patients for *any* indication

I – amoxicillin / co-amoxiclav

C – placebo

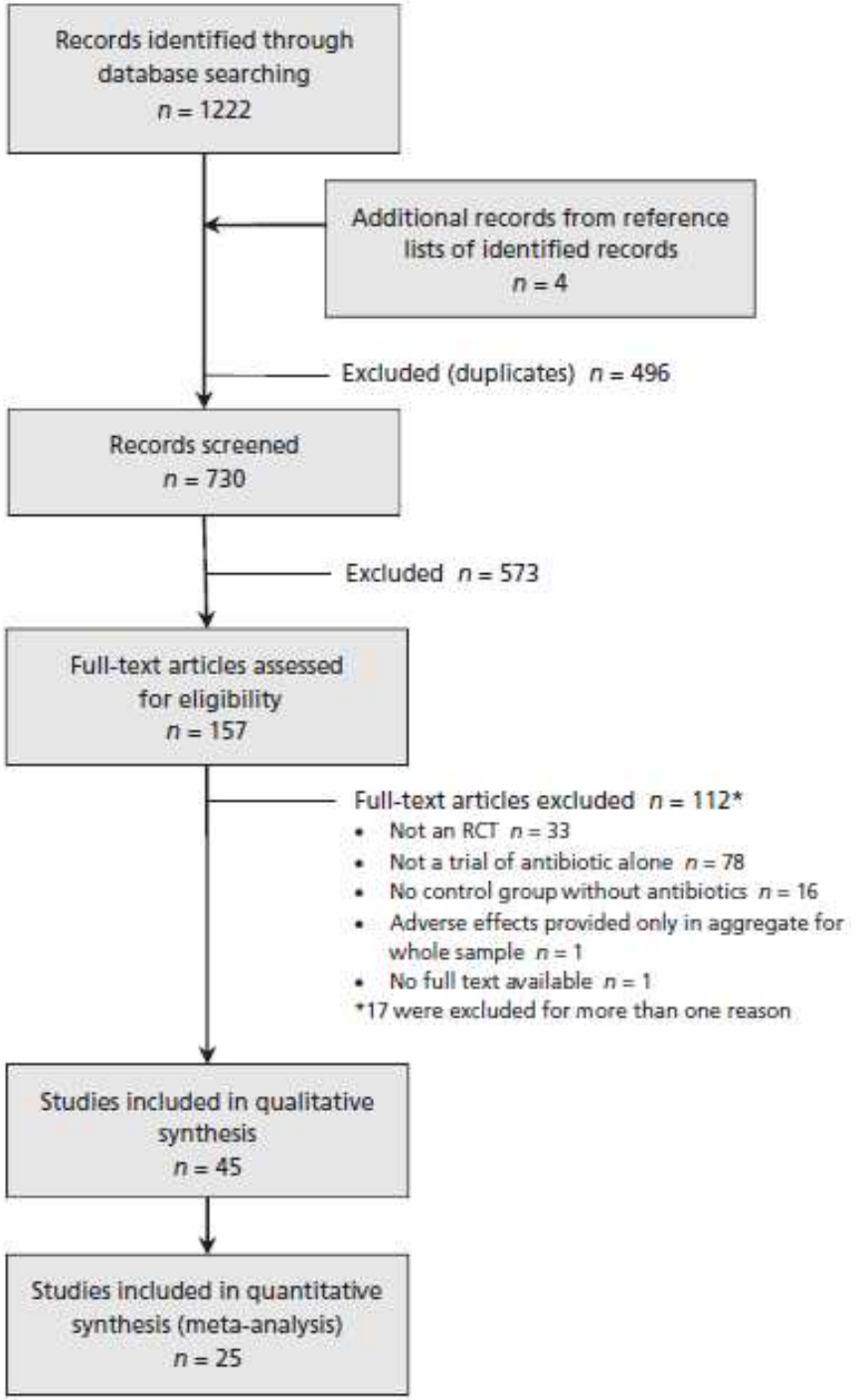
O – *any* adverse events (AEs)

what we did

search

- RCT for *any* indication
- MEDLINE; Embase; Cochrane CENTRAL
- placebo

search



- we discarded all but 45 (27 of amoxicillin and 17 co-amoxiclav)
- 1 trial had both in a 3-arm trial

what we found

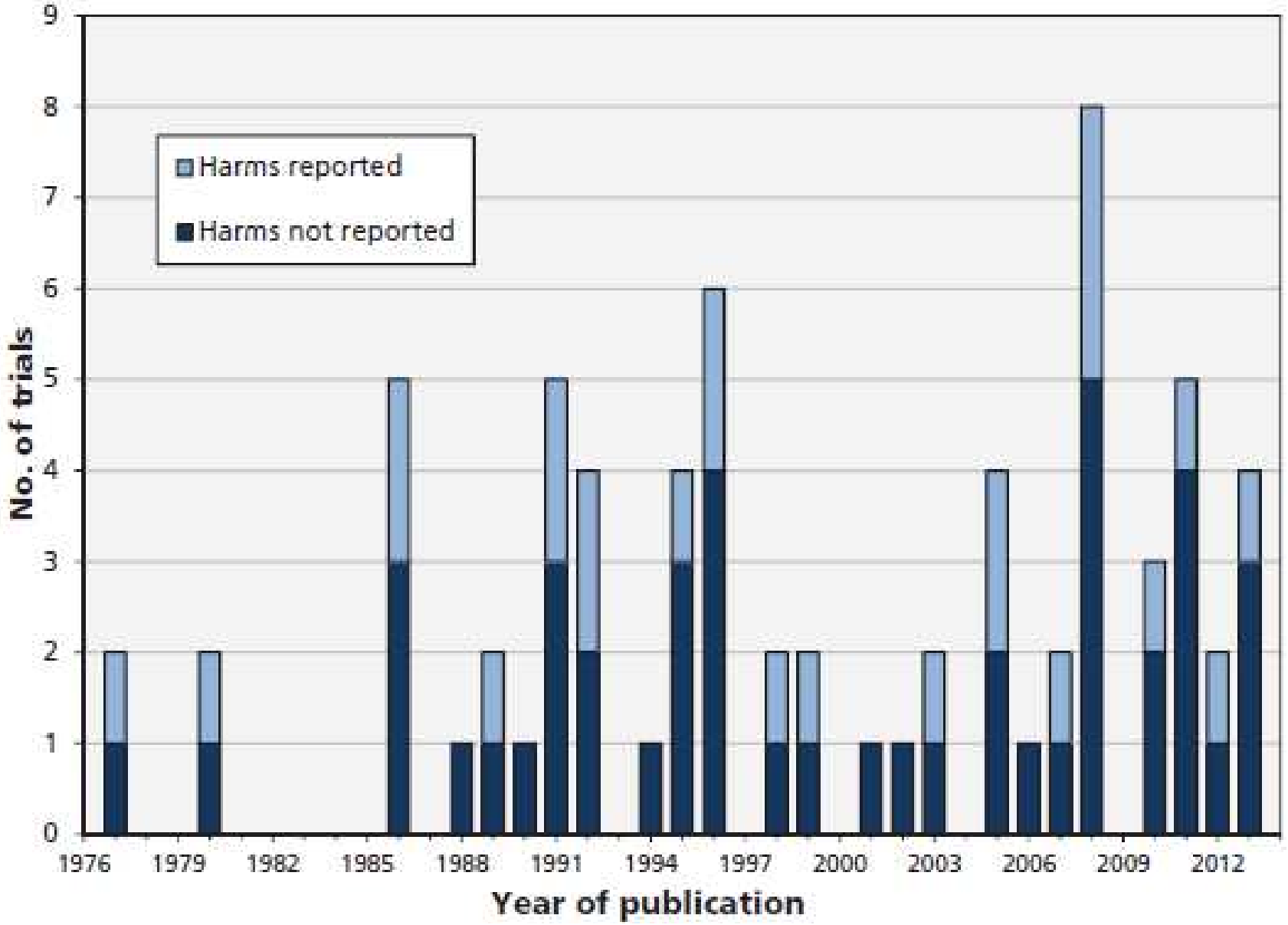
risk of bias… low

…but

only 25/45 trials ➔ harms data

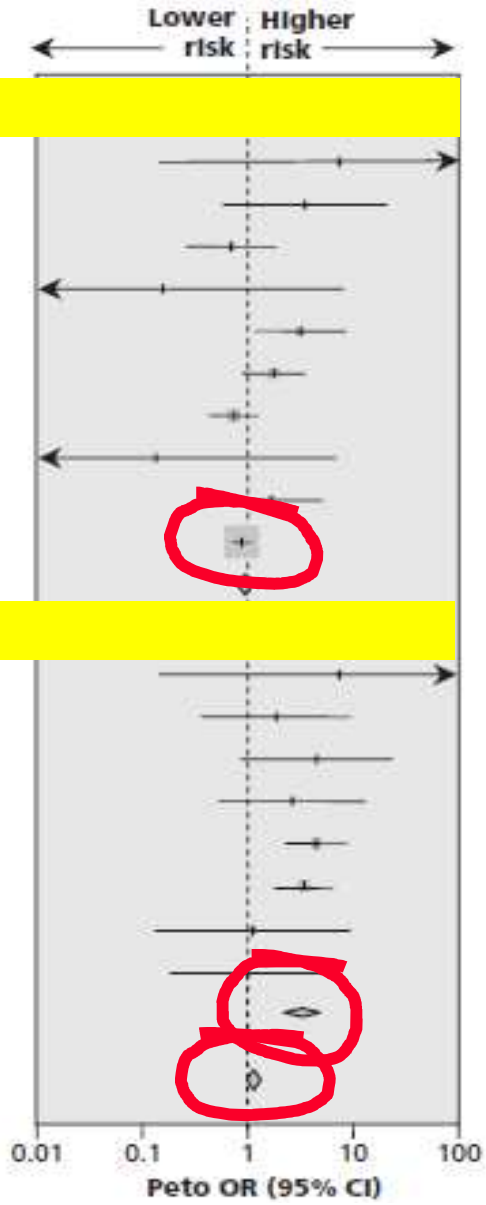
?under-reporting

was reporting better with time?



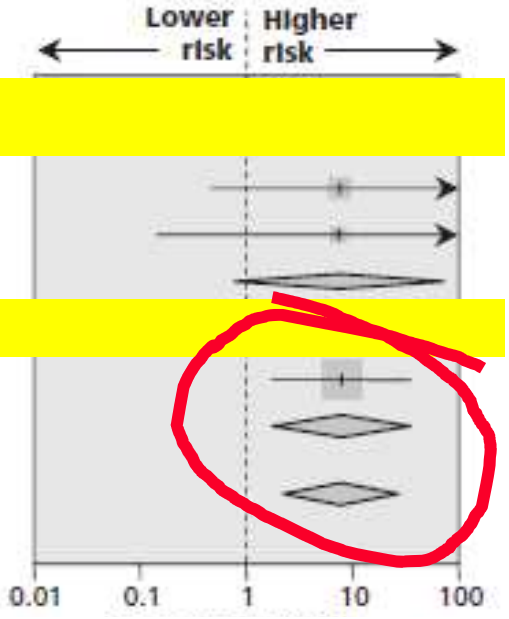
AE = diarrhoea

Study	Antibiotic n/N	Placebo n/N	OR (95% CI)
amoxicillin			
Esposito et al.[41]	1/165	0/165	7.39 (0.15–372.38)
Merenstein et al.[19]	4/67	1/68	3.50 (0.59–20.74)
Meltzer et al.[18]	7/251	10/252	0.70 (0.27–1.83)
Wald et al.[24]	0/41	1/48	0.16 (0.00–7.99)
Jørgensen et al.[11]	13/133	4/137	3.18 (1.19–8.48)
Burke et al.[7]	25/114	16/118	1.77 (0.90–3.48)
Nduba et al.[20]	26/330	34/330	0.75 (0.44–1.27)
Baecher et al.[31]	0/16	1/16	0.14 (0.00–6.82)
Taylor et al.[23]	8/56	6/66	1.66 (0.55–5.05)
Trehan et al.[51]	322/952	352/959	0.88 (0.73–1.06)
Subtotal	406/2125	425/2159	0.95 (0.81–1.12)
amoxi-clav			
Chantelau et al.[49]	1/22	0/22	7.39 (0.15–372.38)
Sclafani et al.[29]	4/86	2/81	1.87 (0.37–9.51)
Wald et al.[24]	5/44	1/48	4.51 (0.87–23.42)
Marchant et al.[17]	5/25	2/25	2.66 (0.55–12.91)
Kaiser et al.[12]	34/146	7/142	4.47 (2.31–8.66)
Hoberman et al.[10]	34/144	11/147	3.42 (1.81–6.45)
Winkel et al.[46]	2/10	2/11	1.12 (0.13–9.40)
Gottfarb et al.[8]	3/26	3/26	1.00 (0.19–5.39)
Subtotal	88/503	28/502	3.30 (2.23–4.87)
Overall	**494/2628**	**453/2661**	**1.14 (0.98–1.33)**



AE = thrush

Study	Antibiotic n/N	Placebo n/N	OR (95% CI)
amoxicillin			
Merenstein et al.[19]	2/67	0/68	7.61 (0.47–123.02)
Nelson et al.[26]	1/15	0/15	7.39 (0.15–372.38)
Subtotal	3/82	0/83	7.54 (0.78–72.88)
amoxi-clav			
Hoberman et al.[10]	7/144	0/147	7.87 (1.76–35.19)
Subtotal	7/144	0/147	7.87 (1.76–35.19)
Overall	**10/226**	**0/230**	**7.77 (2.23–27.11)**

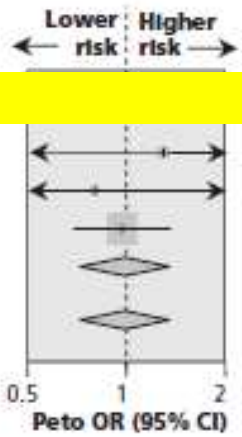


"…diaper-area dermatitis…"

AE = nausea; vomiting

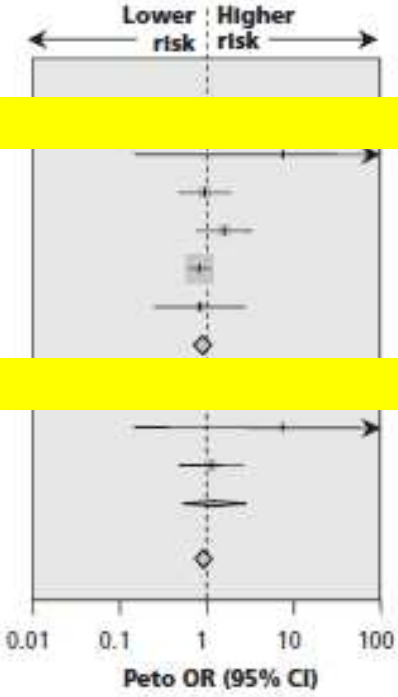
nausea

Study	Antibiotic n/N	Placebo n/N	OR (95% CI)
amoxicillin			
Meltzer et al.[18]	9/251	7/252	1.30 (0.48–3.51)
Merenstein et al.[19]	4/67	5/68	0.80 (0.21–3.09)
Nduba et al.[20]	92/330	94/330	0.97 (0.69–1.36)
Subtotal	105/648	106/650	0.99 (0.72–1.35)
Overall	**105/648**	**106/650**	**0.99 (0.72–1.35)**



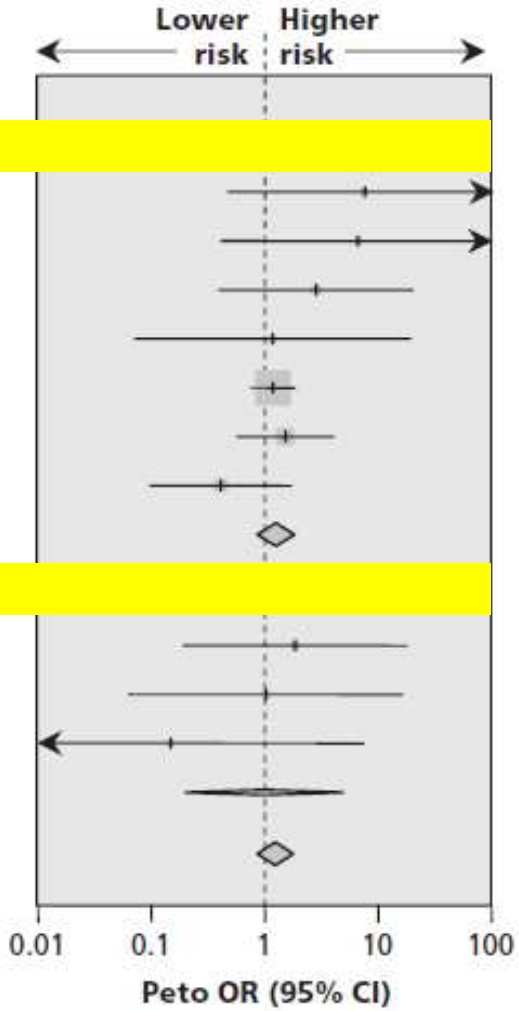
vomiting

Study	Antibiotic n/N	Placebo n/N	OR (95% CI)
Vomiting			
amoxicillin			
Merenstein et al.[19]	1/67	0/68	7.50 (0.15–378.03)
Nduba et al.[20]	17/330	18/330	0.94 (0.48–1.86)
Burke et al.[7]	20/114	14/118	1.57 (0.76–3.25)
Trehan et al.[51]	114/952	137/959	0.82 (0.63–1.06)
Taylor et al.[23]	5/56	7/66	0.83 (0.25–2.73)
Subtotal	157/1519	176/1541	0.89 (0.71–1.12)
amoxi-clav			
Marchant et al.[17]	1/25	0/25	7.39 (0.15–372.38)
Hoberman et al.[10]	12/144	11/147	1.12 (0.48–2.63)
Subtotal	13/169	11/172	1.22 (0.53–2.81)
Overall	**170/1688**	**187/1713**	**0.91 (0.73–1.14)**



AE = rash

Study	Antibiotic *n/N*	Placebo *n/N*	OR (95% CI)
Rash			
amoxicillin			
Merenstein et al.[19]	2/67	0/68	7.61 (0.47–123.02)
Shapiro et al.[37]	2/205	0/182	6.64 (0.41–107.02)
Jørgensen et al.[11]	3/133	1/137	2.83 (0.39– 20.34)
Wald et al.[24]	1/41	1/48	1.17 (0.07–19.23)
Trehan et al.[51]	43/952	37/959	1.18 (0.75–1.84)
Burke et al.[7]	10/114	7/118	1.52 (0.57–4.06)
Taylor et al.[23]	2/56	6/66	0.41 (0.10–1.71)
Subtotal	63/1568	52/1578	1.25 (0.86–1.82)
amoxi-clav			
Sclafani et al.[29]	2/86	1/81	1.85 (0.19–18.04)
Hoberman et al.[10]	1/144	1/147	1.02 (0.06–16.40)
Wald et al.[24]	0/44	1/48	0.15 (0.00–7.44)
Subtotal	3/274	3/276	0.99 (0.20–4.94)
Overall	**66/1842**	**55/1854**	**1.24 (0.86–1.78)**



conclusions 1

search

- RCTs poorly report AEs
- evidence of common AEs for amoxicillin (+/- clavulanate)
  - co-amoxiclav ➔ diarrhoea ~ NNT =10, [95%CI 6-17]
  - Amoxicillin + co-amoxiclav ➔ candida NNT = 27 [95%CI 24-42]
- if poor reporting, then gross under-estimate

Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, Del Mar C. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. Can Med Assoc J. 2014

conclusions 2

search

- this method of quantifying AEs depends on proper reporting in RCTs
- AEs reporting in RCTs must be improved
- data used in Decision Aids
- we are currently reviewing a new set of antibiotics (macrolides and cephalosporins)

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